

# **DAMAGE CONTROL RESUSCITATION: A NEW PARADIGM FOR FLUID RESUSCITATION OF SEVERELY INJURED SOLDIERS**

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## **ABSTRACT**

Recent studies have demonstrated that bleeding disorders are common in the most severely injured trauma patients on admission to the hospital, highlighting the importance of treating this coagulopathy at the earliest stage possible. The concept of damage control resuscitation, which includes hypotensive and hemostatic resuscitation components, was introduced as a new approach to treat these patients at the highest risk of dying. Research studies are being conducted in both experimental animals and with human blood to evaluate different aspects of damage control resuscitation (DCR). Swine models of severe hemorrhage that mimics an uncontrolled hemorrhage have been performed in both anesthetized and sedated pigs (n=8-10/gp) to evaluate short term (3 hr) and long term (72 hr) responses to hypotensive fluid resuscitation with lactated Ringer's, Hextend or fresh whole blood to a systolic blood pressure of 80 mmHg. Human blood was evaluated in vitro to determine the activity of recombinant activated factor VII (rFVIIa), a major adjunct in the DCR guidelines under conditions of hemodilution and hypothermia. The results of the swine studies indicated that whole blood may be best, but where its use is limited by logistic constraints, Hextend should be useful for maintaining a casualty up to a few hours. In addition, in vitro data with rFVIIa suggest that it may be a beneficial adjunct promoting hemostasis in cold, coagulopathic trauma patients, such as those seen at the combat support hospital (CSH), without the need to correct the patient's body temperature prior to the treatment. In addition rFVIIa should also be effective at levels of hemodilution expected in surviving casualties.

## **1. INTRODUCTION**

Hemorrhage remains the leading cause of death in conventional warfare, accounting for about 50% of mortality on the battlefield and 30% of those who die of wounds after reaching a treatment facility (Bellamy, 1984; Champion, 2003). In addition, it is a leading cause of death in civilian trauma (Sawaia et al., 1995). Current dogma dictates that early, adequate fluid resuscitation is crucial to reduce the mortality and morbidity associated with hemorrhagic shock. However, with future combat strategies focused around the Future Force Warrior, greater dispersal of troops and fighting in urban settings and on non-linear battlefields, the likelihood of longer

evacuation times for combat casualties is anticipated. It has been suggested recently that about 17% of military casualties that are killed in action could be rescued with adequate hemorrhage control and fluid resuscitation. However, for the military, resuscitation practice will vary with the echelon of care. On the battlefield or during transportation, Tactical Combat Casualty Care (TCCC) guidelines recommend partial (hypotensive) resuscitation with Hextend for the treatment of injured soldiers the goal is (Dubick and Atkins, 2003; PHTLS, 2005) to raise blood pressure enough to maintain oxygen delivery to tissue as measured by patient consciousness or discernible radial pulse, but not high enough to dislodge clots and increase blood loss. Data from Sondeen et al. (2003) suggest not to raise mean arterial pressure (MAP) above 60 mmHg until hemorrhage control is achieved. This is also a rational approach to compensate for the limited amount of fluid available on the battlefield to treat casualties, and to minimize the chance for rebleeding from penetrating injuries. In addition, studies in experimental animals have suggested that hypotensive resuscitation may improve survival from an uncontrolled hemorrhage (Capone et al., 1995; Stern et al., 2001).

Standard resuscitation practices defined by Advanced Trauma Life Support guidelines (ATLS, 2004) call for a 3:1 volume replacement of lost blood with crystalloid solutions, such as lactated Ringer's (LR) or normal saline, followed serially, by packed red blood cells. Only after 6-10 units of red blood cells are given, is plasma and cryoprecipitate infused (ATLS, 2004). Thus, under standard resuscitation practices that may be coupled with long evacuation times in military situations, it is easy to envision a casualty developing a dilutional coagulopathy resulting from infusion of large volumes of crystalloids (Ho et al., 2005; Roche and James, 2003). However, it is now recognized that derangements in coagulation can occur rapidly as a consequence of traumatic injury itself. For example, it has been reported that up to 34% of civilian trauma patients coming to the emergency department were coagulopathic and had a poor outcome (Brohi et al., 2003; Gonzalez et al., 2006; MacLeod et al., 2003). Coagulopathy associated with trauma has also been observed in military hospitals (Grosso and Keenan, 2000). As this diagnosis is often based on a single laboratory test, the actual incidence may be much higher. In recent data from OIF, all patients requiring massive transfusion were coagulopathic on admission to the

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Combat Support Hospital (CSH) (Repine et al., 2006). Thus, the concept of DCR was developed to address this coagulopathy earlier in the treatment regimen to prevent worsening of trauma-induced coagulopathy by standard resuscitation practices. Thus, together with hypotensive resuscitation practices, DCR at the CSH focuses on avoiding further dilution of coagulation factors in the sickest patients with the highest risk of dying, by using appropriate blood products and limiting the amount of crystalloids, to provide oxygen carrying capability, coagulation factors and sufficient volume to restore tissue perfusion and correct metabolism.

In combat casualties, hypothermia, acidosis, hemodilution and coagulopathy are common and contribute to the "bloody vicious cycle" seen with traumatic injury (Cosgriff et al., 1997; Moore et al., 2004). Evidence from recent conflicts indicates that the incidence of hypothermia is independent of the ambient temperature and occurs with equal frequency in cold and hot climates (COL John Holcomb, personal communication). Hypothermia in trauma patients is known to be an independent risk factor for acute mortality and increases resuscitation fluid requirements (Gentilello et al., 1997) and has been associated with prolonged clotting times and other coagulopathies following traumatic injury (Eddy et al., 2000; Peng and Bongard, 1999). It has been reported that as many as 66% of trauma patients arrive in emergency departments with body temperatures below 36°C (J Holcomb, personal communication).

Recombinant activated factor VII (rFVIIa) is a novel hemostatic agent recommended for treatment of bleedings in hemophiliacs with inhibitors to factors VIII and IX (Gubler et al., 1994). Over the past few years, it has been used "off-label" in patients with uncontrolled bleeding due to trauma and/or massive blood loss, thrombocytopenia, platelet dysfunction or liver dysfunction (Grounds et al., 2006; Payne et al., 2006; Stein and Dutton, 2004). Anecdotal data have shown that rFVIIa significantly reduces the requirement of blood transfusion in trauma and surgery (Martinowitz et al., 2001a). Nevertheless, rFVIIa has become an important component of the DCR strategy.

The studies reported here were conducted with blood from human volunteers or performed in experimental animals to support the DCR strategy. These studies investigated the efficacy of hypotensive resuscitation with fresh whole blood in comparison to LR or Hextend in two severe hemorrhage models in swine. In addition, *in vitro* studies with human blood investigated the efficacy of rFVIIa to impact hemostasis under conditions of hemodilution with LR or Hextend or under hypothermic conditions.

## 2. MATERIALS AND METHODS

### 2.1 Studies with Experimental Animals

In the first experiments, immature female swine (n=8-10/group), weighing about 40 kg, were anesthetized, splenectomized and instrumented with arterial and venous catheters for hemodynamic and blood gas measurements, blood withdrawal and fluid infusion. After baseline recordings each pig was subjected to a controlled hemorrhage of 20 ml/kg over ~5 min that matched the blood loss profile of an uncontrolled hemorrhage as previously described (Dubick et al., 2004). After 30 min a second hemorrhage of 8 ml/kg that followed the same blood loss profile was performed. Fluid resuscitation, using a hypotensive resuscitation strategy, was begun during the second hemorrhage period and was continued to return systolic blood pressure (SBP) to 80 mmHg, as necessary. LR and Hextend were infused at 1.5 ml/kg/min, while fresh whole blood (the animal's shed blood) was infused at 1 ml/kg/min to reduce overshooting the target SBP. All animals were monitored for 3 hr after the start of resuscitation or until death. Hemodynamic variables were monitored continuously throughout the experimental period using strain gauge pressure transducers Model P23XL (Gould Instruments, Oxnard, CA) and the measurements recorded using a Gould polygraph (Gould Instruments, Valley View, CA). Cardiac output was determined continuously using a flow probe placed on the ascending aorta (Transonic Systems Inc, Ithaca, NY). Arterial and venous blood gases were measured continuously using a Trend Care Blood Gas Monitoring System (Diametrics Medical, Inc., Roseville, MN). Blood samples were drawn at baseline (BL), and at 5, 15, 30, 60, 90, 120, 180 and 210 min or at death for determination of plasma lactate, hemoglobin and hematocrit (Hct) by standard clinical chemistry techniques. In the second series of experiments, swine were chronically instrumented using aseptic technique, then allowed to recover. On the experimental day, sedated swine (n=8-10/gp) were hemorrhaged 37 ml/kg and resuscitated with the fluids described above, except hypotensive resuscitation was allowed for 24 hr before swine were fully resuscitated with their shed blood and monitored for an additional 48 hr. Hemodynamics were measured as stated above. Blood samples in these experiments were drawn at BL and 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hr after hemorrhage. Data were analyzed by analysis of variance with repeated measures on time. Post-hoc tests were Bonferroni corrected for multiple comparisons and statistical significance was accepted as  $p < 0.05$ . Categorical data such as survival was analyzed using Fisher's Exact test.

## 2.2 Studies with Human Blood in vitro

For all studies citrated blood samples were collected from 8 healthy volunteers (20-45 years old) after obtaining informed consent and allowed to equilibrate for 30 min. For the hypothermia studies, blood was incubated at 37°, 34°, 31°, and 28 ± 1° C for 30 min. rFVIIa (1.26 µg/ml equivalent to 90 µg/kg *in vivo* dose) or vehicle solution (saline) was added to each blood sample, incubated 10 min, and plasma samples analyzed at their respective temperatures by standard coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen concentrations using the BCS Coagulation Analyzer (Dade Behring, Deerfield, IL) and by thromboelastography (TEG) using the Haemoscope model 5000 (Skokie, IL). For TEG, disposable cups and pins were loaded and allowed to equilibrate to temperature. Next, 10 µl tissue factor (Innovin, diluted 1:500), 20 µl of 0.2 M CaCl<sub>2</sub>, and 4.3 µl of 19.2 µg/ml Corn Trypsin Inhibitor (CTI) were added to each cup and allowed to equilibrate. Then 336 µl of citrated blood was added to each cup and the TEGs were started immediately. The tests were terminated 30 minutes after maximum amplitude (MA) was reached. TEG monitors changes in the viscoelastic properties of blood as a clot is being formed. The measured parameters included clot reaction time (R), clot formation time (K), clot formation rate (α, Angle), maximum clot strength (MA) and time to reach MA (TMA). Calculated parameters include the maximum clotting velocity (Vmax) and time to reach Vmax (t-Vmax). In addition, Hct and platelet levels were measured on a Pentra-120 hematology analyzer (ABX, Montpellier, France). For the hemodilution studies, citrated blood from the human volunteers was equilibrated for 30 min and then diluted to 40%, 60% and 80% with LR or Hextend. rFVIIa was added as above and coagulation assays and TEG analyses were performed at 37° C. Data were analyzed by analysis of variance. If a significant F-statistic was detected, post-hoc tests were performed and Bonferroni corrected for multiple comparisons. A *p* < 0.05 was considered significant.

## 3. RESULTS

### 3.1 Animal Studies

Both hemorrhage models in swine were shown to be 100% lethal with no fluid resuscitation (Dubick et al., 2004; Sondeen et al., 2006). In the short term studies, hypotensive resuscitation to a SBP of 80 mmHg resulted in survival rates of 8/10 in the LR group, 6/8 in the Hextend group and 8/8 in the whole blood group. All fluids were effective in returning and maintaining SBP of 80 mmHg throughout the experiment (Fig 1). However, the volume of fluid required to achieve these levels was

markedly higher in the LR group compared to Hextend and fresh whole blood (83 ± 12 ml/kg compared to 14 ± 5 and 21 ± 3 ml/kg, respectively). Cardiac output (CO) was returned to baseline only in the Hextend-treated animals compared to the other 2 groups, with the lowest CO observed in the whole blood group (Fig 2). Nevertheless, oxygen delivery was similar among the groups (data not shown). Other hemodynamic variables were similarly improved by each fluid after hemorrhage. Metabolic variables, such as base deficit were more improved in the whole blood group compared to the other 2 groups, although there were no significant differences between whole blood and Hextend treated pigs (Fig 3). Plasma lactate concentrations were lower in the whole blood group compared to LR or Hextend groups (Fig 4). As expected, hypotensive resuscitation with whole blood maintained Hct at baseline levels, whereas Hct in the LR or Hextend groups were reduced to about 60% of the baseline level of 33%. Hemodynamic responses to hemorrhage and fluid infusion and changes in lactate levels observed during the 24 hr hypotensive resuscitation period in the second swine experiment, were similar to those observed in the first swine study. Fluid requirements were 90 ± 12, 26 ± 4 and 21 ± 2 ml/kg in the LR, Hextend and whole blood groups, respectively; results similar to those in the first study. Most strikingly, however, 72 hr survival in the whole blood infused group was significantly higher than in both the LR and Hextend infused animals (Fig 5).

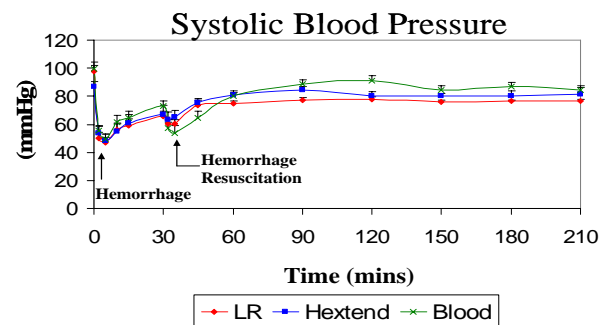


Fig. 1 Systolic blood pressure over time in pigs hemorrhaged at time 0 and at 30 min, and fluid resuscitated.

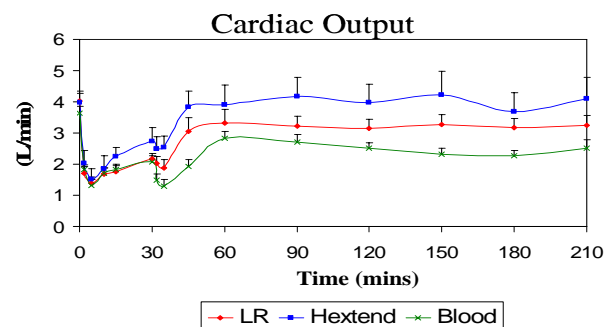


Fig. 2 Cardiac output in response to hemorrhage and fluid resuscitation.

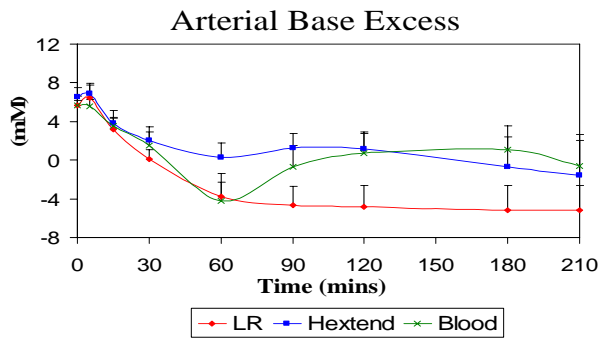
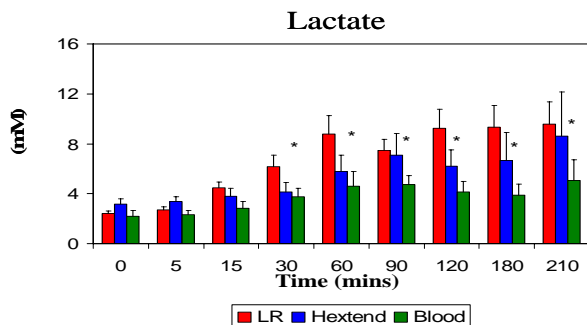


Fig. 3 Calculated arterial base excess in hemorrhaged and fluid resuscitated pigs.



\*  $p < 0.05$  from corresponding LR group

Fig. 4 Plasma lactate concentrations in response to hemorrhage and fluid resuscitation.

#### HYPOTENSIVE RESUSCITATION OF HEMORRHAGIC SHOCK

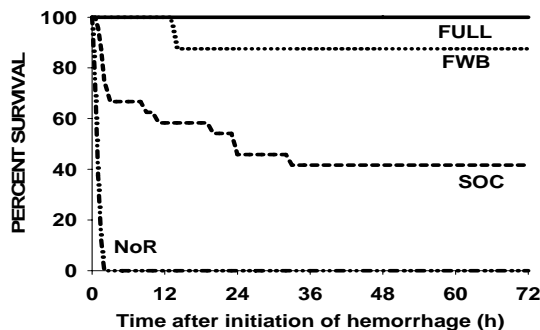


Fig. 5 The survival time was compared for the Standard of Care fluids (SOC: lactated Ringer's and Hextend), and fresh whole blood (FWB) during 24 h of hypotensive resuscitation. Full resuscitation (Full) received LR and all the shed blood within 1 hr; and no-resuscitation (NoR). At 24 h, shed blood was returned to the SOC groups plus 1 L of LR. Animals were then recovered and monitored until 72 h.

### 3.2 Human Studies

In the hypothermia studies, clot reaction times, measured as PT, aPTT, and R time (TEG analysis), were prolonged

at 31°C or below, while the clot formation rate (angle) (Fig 6, 7) and Vmax were decreased at all cold temperatures. Maximum clot strength (MA) was only reduced at 28°C compared to results at 37°C (Fig 6, 7). A similar observation was noted for fibrinogen levels (data not shown). Addition of rFVIIa shortened the PT, aPTT and R times at every temperature, compensating for hypothermic effects with an effect on PT even surpassing the normal (37°C) temperature measurements (Fig 7). Similarly, clot formation rate parameters were also improved by rFVIIa addition and normothermic values were restored in cold blood samples. Vmax and t-Vmax were affected by hypothermia, but rFVIIa improved both variables irrespective of the temperature. MA was the only variable not influenced by rFVIIa (Fig 7).

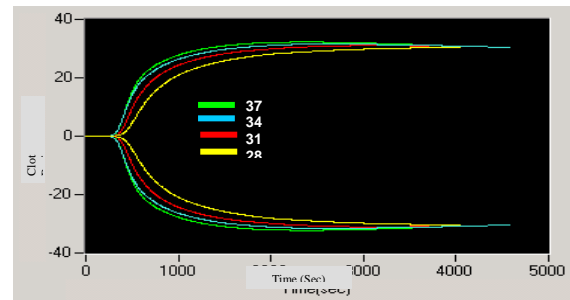


Fig.6 TEG Profile in response to hypothermia in human blood.

Hemodilution resulted in a reduction in fibrinogen and platelet levels that reflected the degree of hemodilution (data not shown). Diluting blood up to 40% had little or no affect on coagulation variables (PT, aPTT and R and K from the TEG), whereas significant prolongation of PT and aPTT were observed at a hemodilution of 80% that was independent of the type of fluid used. TEG revealed that only 80% hemodilution with Hextend prolonged R time, whereas this variable was not affected by hemodilution with LR (Fig 8). K time was prolonged by 60% hemodilution with Hextend, and 80% hemodilution with either fluid (Fig 8). The rate of clot formation (angle) was affected by Hextend at all levels of hemodilution, but only at 80% in the LR group (Fig 8), whereas MA was reduced at all levels of hemodilution with either fluid (Fig 8). Addition of rFVIIa to undiluted blood enhanced coagulation by reducing the R-time and increasing the clotting rate. rFVIIa had a shortening effect on PT and R time at all hemodilution levels evaluated, irrespective of the type of fluid.(Fig 8). However, rFVIIa did not have a significant effect on rate of clot formation or MA at the levels of hemodilution evaluated in this study (Fig 8).

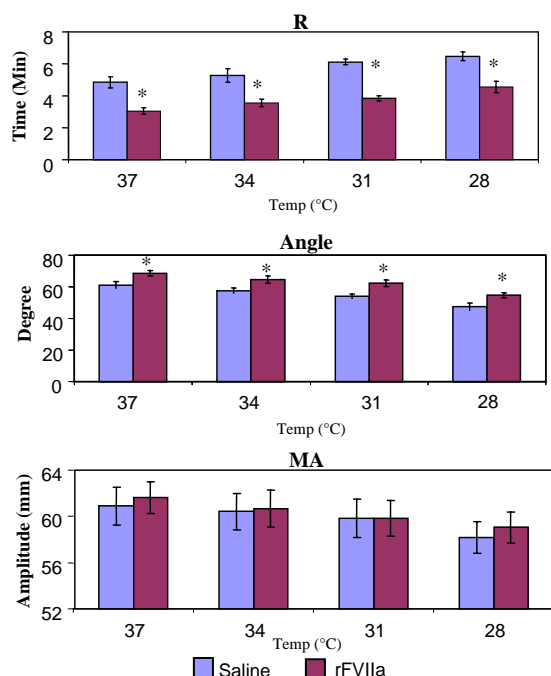


Fig. 7 TEG variable in response to hypothermia and rFVIIa in human blood.

\* Significantly different than Saline control and respective temperature  $p < .05$ .

#### 4. DISCUSSION

As mentioned, the DCR guidelines incorporate the concepts of hypotensive resuscitation and hemostatic resuscitation to provide sufficient volume to perfuse tissue and correct metabolic derangements associated with shock, as well as restore reduced coagulation factors (Hess et al., 2006). Currently in Theater, DCR is being instituted at the CSH with the use of fresh whole blood, judicious use of other blood components such as plasma, packed red blood cells, cryoprecipitate and platelets, limited use of crystalloids and early use of rFVIIa. This DCR protocol is being implemented for the most severely injured casualties (~10% of total) who are coagulopathic and have clinical signs of needing massive transfusion. Preliminary reports on the results of using this DCR protocol from Theater look promising.

The results of the current animal studies indicate that fresh whole blood induced the best overall physiologic improvement. In addition Hextend showed logistic advantage over LR, further supporting its use for far-forward hypotensive fluid resuscitation as part of TCCC for maintaining a casualty up to a few hours. The benefits of whole blood for resuscitation of injured soldiers was reported as far back as World War I (Robertson and Watson, 1918). Over the years its benefit has been

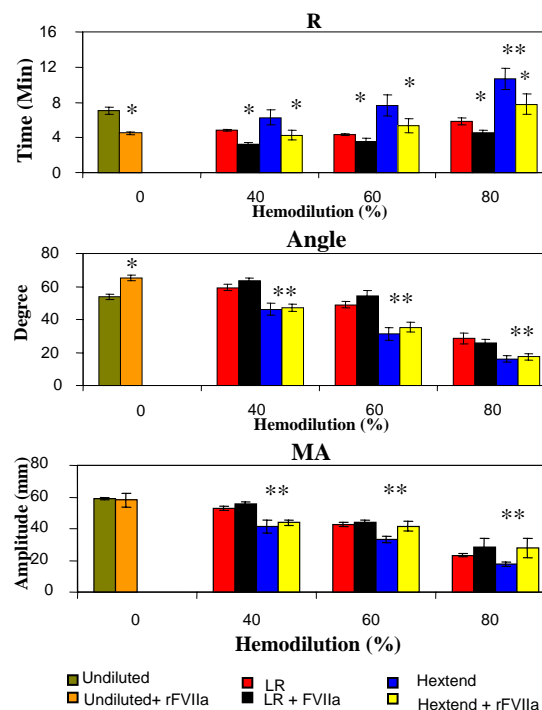


Fig. 8 TEG variables in response to hemodilution and rFVIIa in human blood.

\* Denotes significance ( $p < 0.05$ ) from control (no rFVIIa).

\*\* Denotes significance ( $p < 0.05$ ) from undiluted blood (0).

recognized, but it was also realized that it was not essential for the resuscitation from hemorrhage under the majority of situations (Artz et al., 1955; Shires et al., 1964; Turrano et al., 2001; Wolfman et al., 1963). Recently, with the recognition of trauma-induced coagulopathy in severely injured patients, the interest in whole blood as a resuscitation fluid has gained renewed interest (Kauvar et al., 2006; Malsby et al., 2005; Repine et al., 2006). Further research in this field will help define the optimal use of whole blood in trauma patients. Enthusiasm in the off-label use of rVIIa in trauma patients has been spurred by initial anecdotal and case reports of spectacular results in hemorrhaging patients (Kenet et al., 1999). These initial findings were later supported by more controlled clinical trials (see (Holcomb, 2005; Rizoli and Chughtai, 2006)). Its use in treating hemorrhaging trauma patients is attractive because it offers a site-specific therapy for controlling hemorrhage, via its tissue-factor binding mechanism (Martinowitz et al., 2001a & refs cited therein). Reports suggested that rFVIIa reduced post-treatment blood loss, but effects on outcome were less clear (Grounds et al., 2006). As use of rFVIIa in the treatment of trauma increased, reports of its failure to stop bleeding have emerged and efforts have been made to determine conditions in which rFVIIa would not be

effective or limits of its effectiveness (Bowles et al., 2006; Stein et al., 2005). In the present study, in vitro studies with human blood were undertaken to determine limitations of the effectiveness of rFVIIa under conditions that might be encountered in the treatment of trauma patients. We first evaluated hemodilution which might occur when a casualty is treated with large amounts of crystalloids or crystalloids and red blood cells as part of standard ATLS-guided fluid resuscitation (ATLS 2004; Roche and James, 2003). Hemodilutions of 50-60% have been commonly employed as models of coagulopathy (Fries et al., 2005; Holcomb et al., 1999). In addition, it was previously reported that a hemodilution of 40% may be encountered in patients expected to survive (Wade et al., 1996). The results of the present study with human blood in vitro are consistent with previous reports of effects on coagulation function by hemodilution. The present results also indicate that LR or Hextend would not be expected to induce significant effects on coagulation at standard doses used for resuscitation.

The present study also evaluated the effects of hypothermia on the activity of rFVIIa in vitro. We observed that rFVIIa was able to improve coagulation even at temperatures as low as 28°C; temperatures associated with cardiac arrhythmias and death in trauma patients (Jurkovich et al., 1987). These results are also consistent with many in vivo studies in experimental animals showing rFVIIa effectiveness in cold, coagulopathic animals or patients (Martinowitz et al., 2001b; 2004; Schreiber et al., 2002).

## 5. CONCLUSION

Damage control resuscitation is a strategy to provide effective resuscitation to the most severely injured casualties entering the CSH. The results of the present studies in swine demonstrated the effectiveness of fresh whole blood, but also showed that limited use of Hextend could be effective for about 5 hours for casualties expecting long evacuation times. In addition, the present in vitro studies support the use of rFVIIa as a beneficial adjunct promoting hemostasis in cold, coagulopathic trauma patients, such as those seen at the CSH, without the need to correct the patient's body temperature prior to the treatment. In addition rFVIIa would also be effective at levels of hemodilution expected in surviving casualties. Thus, in our efforts to help sustain and improve survival of the Future Force Warrior, these studies support the new strategy of damage control resuscitation for treating severe hemorrhage, being implemented in current Theaters of Operation. Future studies will further define the beneficial properties of blood components to move damage control resuscitation practices to forward echelons of care.

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